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Phase III randomised trial

Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial

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ABSTRACT

Purpose: To assess the impact of the boost dose in patients with involved surgical margins.
Patients and methods: In the EORTC "boost versus no boost" trial, 251 patients with a microscopically incomplete tumour excision were randomised to receive either a low boost dose of 10 Gy (126 patients) or a high boost dose of 26 Gy (125 patients). Overall survival and the cumulative incidence of local recurrence as first event were compared by Logrank and Gray test, respectively (2-sided $\alpha = 0.05$), with a median follow-up of 11.3 years. The planned sample size was 660 patients, but only 251 were recruited.
Results: The median age at randomisation was 54 years. Thirty-seven patient initially relapsed locally. At 10 years, the cumulative incidence of local recurrence was 17.5% (95% CI: 10.4–24.6%) versus 10.8% (95% CI: 5.2–16.4%) for the low and high boost dose groups, respectively (HR = 0.83, 95% CI: 0.43–1.57, Gray $p > 0.1$). Overall, 64 patients have died (25.5%), 47 of them of breast cancer, without a difference in duration of survival between the two groups (HR = 0.97, 95% CI = 0.59–1.5, $p > 0.1$). Severe fibrosis was palpated in the breast in 1% versus 5% and in the boost area in 3% versus 13% in the low and high boost dose groups, respectively.
Conclusions: There was no statistically significant difference in local control or survival between the high boost dose of 26 Gy and the low boost dose of 10 Gy in patients with microscopically incomplete excision of early breast cancer. Fibrosis, however, was noted significantly more frequently in cases treated with the high boost dose.
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Breast-conserving therapy (BCT) is considered the standard of care for stage I and II breast cancer patients, with equivalent survival compared to mastectomy [1–3]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis confirmed the need for radiotherapy after lumpectomy, by showing that breast irradiation reduced the 5-year local recurrence rate from 26% to 7% [4]. In the EORTC (European Organisation for Research and Treatment of Cancer) trial 10801 that compared BCT with mastectomy, two major limitations were identified, despite similar survival rates and a limited difference in local control between the two treatment arms [3]. First, a significant proportion of the patients experienced severe fibrosis that resulted in a poor cosmetic outcome because of the high radiation dose given [5]; second, major differences in local control were observed between the treating institutes, which could not be explained by patient selection [6].

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Meanwhile, Van Limbergen et al. demonstrated the dose-dependency of local control, suggesting a decrease in the local failure rate by a factor of two for every 15 Gy increase in dose [7]. Against this background, the EORTC launched a subsequent prospective randomised trial (EORTC 22881-10882 "boost" trial), investigating the relevance of a boost dose to the primary tumour site after lumpectomy and whole breast irradiation (50 Gy in 25 fractions over 5 weeks). In this randomised phase III trial patients who underwent a microscopically complete tumour excision received either a boost or no boost. The boost dose was 16 Gy, because of the large proportion of patients who developed fibrosis with 25 Gy boost in the earlier trial. The 10-year results demonstrated that this boost dose reduced the local recurrence rate by 41% (10.2% versus 6.2%), without a difference in survival [8].

For many years, the association between positive resection margins and local recurrence after BCT has been controversial but, in general, they are considered as a relevant poor risk factor for developing a local recurrence after BCT [7,9,10]. Whereas the optimal resection margin is uncertain, surgery should always aim at removing the whole tumour including a margin of surrounding breast issue. That this is not always successful is illustrated in the EORTC "boost" trial, where in about 15% of the cases the resection margins of the first lumpectomy turned out to be involved by tumour. In most cases, a second excision can make the resection complete but often surgical factors and the expected cosmetic outcome make this impossible. Whereas a mastectomy is often proposed to the patients, this is not always accepted and might even be considered as unnecessary. A large number of factors have an influence on the risk of an incomplete lumpectomy, including patient and tumour related factors such as the size and location of the tumour within the breast, the volume of the breast and thereby the amount of normal breast issue surrounding the tumour that can be removed, and histological factors with especially a high risk for invasive lobular carcinoma and in the presence of an extensive intraductal component [11]. Surgical factors might play an important role as well, including the experience of the surgeon and the availability of technical solutions to guide the lumpectomy especially in the case of smaller not palpable lesions. Whether the higher local recurrence risk after an incomplete tumour excision can be completely counterbalanced by increasing the boost dose has not been demonstrated clearly. Therefore, we randomised in the EORTC 22881-10882 "boost" trial patients with a microscopically incomplete resection of the primary tumour (as stated by the local pathologist) between a low boost dose of 10 Gy, supposedly associated with a better cosmetic outcome, and a high boost dose of 26 Gy, supposedly achieving a better clinical control at the cost of possible increased fibrosis and less satisfactory cosmetic outcome. The trial objectives for this subgroup were therefore primarily to assess the impact on local control and how much the potential difference in local control is counterbalanced by an increased fibrosis.

Patients and methods

Patients up to 70 years with T1-2, N0-1, and M0 breast cancer were eligible for this trial [12]. Patients with pure carcinoma in situ (CIS), multiple tumour foci in more than one quadrant, a history of other malignant disease, a WHO performance score $\geqslant 2$, residual micro-calcifications on mammography or gross residual disease in the breast after lumpectomy (unless re-excision had been performed) were ineligible. Oral informed consent was obtained according to EORTC guidelines and the local and national rules of the participating centres.

Surgery preceded referral for radiotherapy and consisted of excision of the primary tumour, with a 1-cm margin of macroscopically normal tissue, and an axillary lymph node dissection. Any removal of additional breast tissue after the excision of the primary tumour was scored as a re-excision, whether it was performed during the same session or later. The resection margins were evaluated by the local pathologist for the presence of invasive carcinoma and for DCIS, without any further specification of the extent of the involvement. Patients with gross tumour involvement or with residual micro-calcifications on a postoperative mammography were not eligible. A subset of 1725 patients had a central pathology review of their slides. Patients with involved axillary lymph nodes received adjuvant systemic therapy, consisting of chemotherapy for pre-menopausal patients and tamoxifen for postmenopausal patients. Radiotherapy started not later than 9 weeks after lumpectomy, unless adjuvant chemotherapy was given first. Irradiation of the whole breast was performed using two tangential megavoltage photon beams (photons or cobalt-60). A total dose of 50 Gy over a 5-week period, with a dose of 2 Gy per fraction, was delivered at the intersection of the central axes of the beams, according to the ICRU 50 report [13]. Two off-axis dose distributions in the tumour excision area and cranial and caudal border planes had to be calculated as well. The boost dose had to be specified at the centre of the surgical tumour bed. This dose remained fixed and independent of the dose actually delivered to the boost area during the external irradiation of the whole breast. The boost dose had to be delivered with electrons or tangential fields given in daily fractions of 2 Gy, or with an iridium-192 implant at a dose rate of 0.5 Gy per hour. The boost volume was described as the site of the primary tumour with a margin of 1.5 cm to the field borders after a complete lumpectomy and of 3 cm after an incomplete resection or in the presence of an extensive intraductal component [14]. An intensive Quality Assurance programme for radiotherapy was organised to ensure that the treatment was delivered according to the guidelines described in the protocol in all centres [15].

Randomisation was done after surgery and centrally at the EORTC Head Quarters using the minimisation technique [16]. Treatment allocation was balanced with respect to age, menopausal status, presence of extensive DCIS (when 10 or more ducts were involved, the DCIS component was classified as such), clinical tumour size, nodal status, and institute where they received radiotherapy. The patients with complete tumour excision were allocated no boost or 16 Gy boost, the patients with incomplete excision were separately allocated a 10 Gy boost or a 26 Gy boost.

All analyses were carried out according to the intent-to-treat policy, i.e. all randomised patients are included in the analyses in the arm they were assigned by randomisation. Time to local recurrence was calculated from the date of randomisation to the date of recurrence. Local recurrences in the breast as the first failure were analysed. Data for patients who remained free of local disease were censored at the date of last visit, but any other failure as the first event was considered as a competing risk. Survival and local failure rates were estimated by Kaplan–Meier and by cumulative incidence, respectively [17,18]. The 2-sided significance level was set at 0.05. Treatment effects are summarised by the hazard ratio estimated from unadjusted Cox regression models and its associated 95% confidence interval.

In the original protocol, 660 patients with incomplete excision were planned to be recruited and followed for 10 years, with the aim to exclude a loss of 5% or more in the 10-year local control rate with the low boost dose compared to the high boost dose, at the 1-sided 5% significance level. The second objective was to evaluate a possible difference in the development of fibrosis in the treated breast. However, the study duration was driven by the complete